Review: new anti-cytokines for IBD: what is in the pipeline?

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Abstract: Significant advances have been achieved in the understanding of the pathogenesis of inflammatory bowel disease (IBD). A number of susceptibility genes have been detected by large genome wide screening-approaches. New therapeutic concepts emerge from these insights. The most important progress in recent years certainly is the introduction of biologics in the therapy of IBD. TNF blockers have been shown to be very effective for the control of complicated disease courses. Currently, in addition to the three already established anti-TNF antibodies, new anti-TNF molecules, for example Golimumab, are in clinical trials and also reveal promising results. However, not all of the patients respond to anti-TNF treatment and many patients lose their response. Therefore, additional therapeutic approaches are urgently needed. Attractive therapy targets are cytokines as well as their receptors and signaling pathways. At the moment a large number of biologicals and inhibitors are tested in clinical trials and some of them provide very promising results for the treatment of IBD patients. In particular, inhibition of IL-12p40 by specific antibodies as well as of the janus kinase (JAK)3 by a small molecule promise to be very effective approaches. Though antibodies targeting for example IL-6, IL-6R, IL-13 or CCR9 are only in the early steps of clinical development, they have already demonstrated to be a possible treatment option which needs to be confirmed in further trials. Taken together a large number of new therapeutic anti-cytokine approaches are currently tested in clinical trials in IBD patients. In this review, the new therapeutic approaches for cytokine inhibition in IBD patients are discussed.

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Review: New anti-cytokines for IBD: what is in the pipeline?

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Summary

Significant advances have been achieved in the understanding of the pathogenesis of inflammatory bowel disease (IBD). A number of susceptibility genes have been detected by large genome wide screening-approaches. New therapeutic concepts emerge from these insights. The most important progress in recent years certainly is the introduction of biologics in the therapy of IBD.

TNF blockers have been shown to be very effective for the control of complicated disease courses. Currently, in addition to the three already established anti-TNF antibodies, new anti-TNF molecules, for example Golimumab, are in clinical trials and also reveal promising results. However, not all of the patients respond to anti-TNF treatment and many patients lose their response. Therefore, additional therapeutic approaches are urgently needed. Attractive therapy targets are cytokines as well as their receptors and signaling pathways. At the moment a large number of biologicals and inhibitors are tested in clinical trials and some of them provide very promising results for the treatment of IBD patients. In particular, inhibition of IL-12p40 by specific antibodies as well as of the janus kinase (JAK)3 by a small molecule promise to be very effective approaches. Though antibodies targeting for example IL-6, IL-6R, IL-13 or CCR9 are only in the early steps of clinical development, they have already demonstrated to be a possible treatment option which needs to be confirmed in further trials.

Taken together a large number of new therapeutic anti-cytokine approaches are currently tested in clinical trials in IBD patients. In this review, the new therapeutic approaches for cytokine inhibition in IBD patients are discussed.

Keywords: Anti-cytokine antibodies, biologicals, Crohn's disease, cytokines, inflammatory bowel disease, ulcerative colitis,

Introduction

Inflammatory bowel disease (IBD) represents a chronic intestinal inflammation and is comprised of its two major forms, Crohn's disease (CD) and ulcerative colitis (UC). The pathogenesis of IBD involves a complex interplay between genetic susceptibility of the host, external environmental factors, the internal intestinal microbiota, infectious particles and a dysregulated immune system. Current hypothesis suggests that an epithelial barrier defect in a genetically susceptible host results in an aberrant immune response to environmental and "in-vironmental" factors[1, 2]. In particular, the aberrant immune response involves both, the innate as well as the adaptive immune system providing a large number of pro- and anti-inflammatory cytokines as possible causative as well as disease-promoting molecules in IBD pathogenesis. Being involved in intestinal inflammation these cytokines have been selected as treatment targets. A further and also a very promising approach seem to be anti-adhesion molecule strategies, for example $\alpha_4\beta_7$-integrin inhibitors, such as Vedoli-

zumab. However, as this review was intended to focus on anti-cytokine therapies those promising anti-adhesion approaches are not further featured in this review.

Cytokines are produced by lymphocytes (especially by T-cells of the Th1, Th2 and Th17 phenotype), monocytes, intestinal macrophages, granulocytes, epithelial cells, endothelial cells, and fibroblasts. They have pro-inflammatory (interleukin (IL)-1, tumor necrosis factor (TNF), IL-6, IL-8 or IL-12) and/or anti-inflammatory (IL-1 receptor antagonist [IL-1ra], IL-4, IL-10, IL-11 or transforming growth factor ß [TGFß]) functions.

Mucosal and systemic concentrations of many pro- and anti-inflammatory cytokines are elevated in IBD patients[3]. For example, an imbalance between pro-inflammatory and anti-inflammatory cytokines was found for the IL-1/IL-1ra ratio in the inflamed mucosa of patients with CD, UC, diverticulitis and infectious colitis[4]. Furthermore, inhibition of pro-inflammatory cytokines or supplementations with anti-inflammatory cytokines reduced inflammation in animal models of colitis, such as the dextran-sulfate sodium (DSS) colitis model, the trinitrobenzene sulfonic acid (TNBS) model or the genetically engineered IL-10 knock-out colitis model[5, 6, 7, 8, 9].

To obtain a complete as possible overview of all of the current strategies to target cytokines and cytokine-related signaling, we performed a computerized systemic search of English language publications in the PubMed, Cochrane Library, European Medicines Agency and the Food and Drug Administration databases as well as current clinical trial databases (www.nih.gov and www.clinicaltrials.gov) until January 2013. The following search terms were applied: “Crohn’s disease” or “inflammatory

bowel disease" or "ulcerative colitis" and "biologicals" or "biological" or "anti-cytokine therapy".

Cytokines as drug targets in IBD

The inflammatory pattern in CD has been associated with enhanced occurrence of T-helper (Th)1 and Th17 cells, while the T-cell signature of UC is more similar to a Th2 cell disease type[1, 10]. The development of Th1 and Th17 cells in CD is triggered by inflammatory mediators, such as IL-12, IL-18, IL-23 and TGFβ that are secreted by antigen presenting cells (APC) and macrophages[11]. Presence of these Th-cell subsets results in elevated levels of the pro-inflammatory cytokines IL-2, IL-17, TNF and IFNγ in the serum as well as in the intestinal mucosa of CD patients, what finally causes secretion of TNF, IL-1β, IL-6, IL-8, IL-12 and IL-18 from APC, macrophages, fibroblasts, endothelial and epithelial cells. These events promote ongoing inflammation and finally establish the secretion of pro-inflammatory cytokines as a vicious circle[12, 13, 14, 15]. As mentioned, mucosal inflammation in UC has a pattern of cytokine secretion that is similar to the pattern secreted by the Th2 cell-type including increased levels of IL-4, IL-5 and IL-13[16]. Vice versa IL-4, IL-5 and IL-13 promote Th2 cell differentiation which further may augment levels of IL-13[16, 17]. T-cells can also be directly activated via antigen presentation by APC. Anti-inflammatory cytokines, such as IL-10, are also important in modulating T-cell activity.

Based on these findings the rationale for cytokine-modulating treatment of IBD patients was defined (Figure 1). Different strategies like the inhibition of pro-inflammatory cytokines or the administration of anti-inflammatory cytokines led to some promising results. In general there are three different mechanism of anti-cytokine treatment possible: First, an antibody or inhibitor that targets the cytokine directly. Secondly, an antibody or inhibitor of the respective cytokine receptor and thirdly, a molecule that inhibits signaling pathways that are crucial for mediating cytokine-induced effects by targeting intracellular signaling molecules. Thirdly, the administration of anti-inflammatory cytokine seems to be a promising approach. However, so far, only two cytokines, namely TNF and the p40 subunit of IL-12/IL-23, have been proven to be successful targets for treating IBD patients. To date, anti-TNF antibodies are the only anti-cytokine antibodies that have been approved in IBD. Additionally, ustekinumab an antibody targeting the p40 subunit of IL-12/IL-23 is currently about to be approved for treatment of CD after excellent results in clinical phase IIb trials. For example, in contrast to anti-TNF treatment, targeting of IFNγ using the antibody fontolizumab finally failed in placebo-controlled clinical studies to show a significant clinical benefit in CD patients[18, 19, 20].

There are a large number of studies ongoing investigating a possible beneficial effect of anti-cytokine treatment in IBD patients, such as therapies targeting TNF, IL-6, IL-6 receptor (IL-6R), IL-12, IL-23, IL-17A, IL-18, anti-C-C chemokine receptor type 9 (CCR9) or anti-C-X-C motif chemokine 10 (CXCL10) (Table 1). The

respective medications are either biological agents or small molecule inhibitors. Though biological medications feature some advantages, such as potency of action and specificity, what might reduce their off-target side effects, they also exert certain disadvantages, such as immunogenicity, high costs or a long half-life, what might result in prolonged immunosuppression and infectious complications. Further, though treatment with anti-TNF antibodies is successful in a certain number of patients, only up to 50 % achieve steroid free remission and some of them will even lose their response after a certain period of time[21, 22, 23]. Therefore, it is obvious that new therapeutic strategies targeting cytokines in IBD need to be developed.

New biologicals directed against cytokines

New anti-TNF strategies

In 1997 the first successful study using an anti-cytokine approach was published showing the efficacy of the anti-TNF antibody, infliximab, in patients with CD[24]. In the meantime, two more anti-TNF antibodies have been approved for treatment of CD, namely adalimumab and certolizumab pegol. Further, infliximab and adalimumab are also approved for treatment of UC in the US and the EU. However, not all of the tested anti-TNF approaches are effective. Namely the p75 TNF soluble receptor fusion protein etanercept[25], the IgG4 monoclonal anti-TNF antibody CDP571[26], the p55 TNF soluble receptor monomer onercept[27] or the small molecule semapimod (CNI-1493)[28] failed in clinical trials. For example, etanercept, a genetically engineered fusion protein consisting of two identical chains of the recom-

binant human TNF-receptor (TNF-R) p75 monomer fused with the Fc domain of human immunoglobulin (Ig) G1 that binds and inactivates TNF, failed to show a clinical benefit in IBD patients[25]. In contrast, while etanercept is approved and very efficient in the therapy of RA, thee observations demonstrate that results obtained in clinical trials with RA patients cannot be directly translated to IBD patients. Also, unfortunately up to 40% of CD patients do not have a sufficient response to anti-TNF treatment and are so-called “primary non-responders” and others develop antibodies against monoclonal antibodies leading to treatment modification and discontinuation[21, 22, 23].

Golimumab

Golimumab is a fully human monoclonal IgG-1 anti-TNF antibody under investigation for moderate to severe UC. The approved dose is 50mg subcutaneously once a month. It is licensed for the treatment of rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis[29]. Results of the phase II/III PURSUIT trial, reported at Digestive Disease Week (DDW) 2012, showed significantly higher UC clinical response and remission rates with this anti-TNF agent compared with placebo, improvements that were maintained throughout the 54-week study period[30]. In this large trial safety and efficacy was evaluated in moderately to severely active UC. All trial patients had failed to respond to or tolerate treatment with 6-mercaptopurine, azathioprine, corticosteroids or 5-aminosalicylates or were steroid dependent. Study patients were naïve to treatment with TNF-antibodies. The trial had an adaptive de-

sign with Phase 2 dose ranging followed by a confirmatory phase 3 component. Patients were randomized to receive golimumab 100 mg/50 mg (prior to dose selection only), placebo or golimumab 200 mg/100 mg or 400 mg/200 mg at weeks 0 and 2. The primary endpoint was clinical response at week 6. Secondary endpoints at week 6 included clinical remission, mucosal healing and a change from baseline in IBDQ scores. Overall, 1065 patients were treated in the study; 774 of these patients were randomized into the Phase 3 component of the study. Patients responding to induction treatment with golimumab were eligible to continue in the Phase 3 PURSUIT maintenance study. At week 6, a clinical response was observed in 45% to 57% of golimumab-treated patients (across dosing groups) compared with 31% of patients on placebo. A significant trend toward improved mucosal healing was also observed. Adverse events in the golimumab groups included 1 death due to peritonitis, 1 case of demyelination, and 1 colon cancer (detected in screening biopsies). No serious infections were reported, and the safety profile was consistent with those of other anti-TNFs in inflammatory bowel disease (IBD) and of golimumab for rheumatologic indications. Due to its subcutaneous application, efficacy and tolerability, golimumab might be an interesting option for outpatients suffering from moderate to severe colitis.

TNF-Kinoid

An attractive alternative therapeutic strategy is active anti-TNF immunization using TNF-Kinoid. TNF-Kinoid is a formulation in which human TNF is coupled to

keyhole limpet hemocyanin (KLH) as a carrier protein, inactivated and emulsified with MONTANIDE ISA 51 VG. It was developed by Neovacs SA; France. In a phase I-II dose escalation study it was administered intramuscularly on day 0,7 and 28 with a maintenance dose on day 168 in thirteen patients with moderate to severe Crohn's disease[31]. Patient's developed an anti-TNF antibody response that peaked within weeks and at week 4 and 12 36% and 54% of the patients demonstrated a clinical remission (CDAI < 150) with a relevant decrease of calprotectin levels in stools. These promising results need further studies to confirm efficacy, safety and tolerability.

Ozoralizumab (ATN-103)

Ozoralizumab (ATN-103) is a trivalent albumin-binding nanobody that neutralizes TNF. A nanobody is an antibody fragment (single domain antibody) that is, similar as a complete antibody, able to bind selectively to a specific antigen. ATN-103 is currently in multi-center phase II trials against rheumatoid arthritis. It showed excellent safety and efficacy results in a 48-week phase II open-label study in rheumatoid arthritis patients who had insufficient response to methotrexate alone[32]. Ozoralizumab was administered by a subcutaneous injection every four weeks.

DLX105

DLX105 is a new type of an anti-TNF optimized single-chain F_v monoclonal antibody which is developed for topical treatment in patients with chronic in-

flammatory disorders, such as chronic skin inflammation, osteoarthritis and CD. The advantage is that DLX105 can be administered locally and presents hardly any systemic resorption. A currently ongoing placebo-controlled phase I/IIa study analyses the efficacy of DLX105 when injected directly into the fistula tracts of CD patients.

Anti Interleukin-6 strategies

Similar to TNF, the pleiotropic cytokine IL-6 also appears to play a pivotal role in the pathogenesis of IBD. IL-6 is produced by a large number of different cell types and secretion is induced during acute phase response. The major sources of IL-6 in the gut are macrophages whereas the results on secretion of IL-6 by epithelial cells are conflicting. IL-6 exerts its physiological functions not only via its membrane-bound IL-6 receptor (IL-6R), which is limited to a small number of cell types, such as hepatocytes or monocytes/macrophages, but also via its soluble IL-6 receptor (sIL-6R). This way, IL-6 can signal to all body cells since the respective IL-6/sIL-6R complex binds to the ubiquitously expressed receptor-subunit gp130[33, 34, 35]. IL-6 serum levels correlate with disease activity of both, CD and UC, and upon anti-inflammatory treatment, IL-6 serum levels decline correlating to the decrease in disease activity[36, 37]. The induction of C-reactive protein (CRP) is the liver is mediated by IL-6. Also serum levels of sIL-6R are elevated in IBD patients and correlate with disease activity[38].

Several studies also indicated a predictive value for IL-6 serum levels with respect to the detection of a CD relapse suggesting that IL-6 serum levels might

be a useful marker for disease monitoring. High IL-6 levels are associated with an increased risk for relapse[39, 40]. Monitoring of IL-6 serum levels also reflects the clinical response to steroid treatment and predicts clinical relapse after steroid-induced remission[41, 42]. Additionally, a polymorphism within the IL-6 gene locus has been associated with early onset CD and persistent activation of the IL-6 signaling pathway is associated with the development of colorectal cancer[43, 44, 45, 46]. Due to these observations IL-6 is regarded to be a promising target for the treatment of IBD.

Currently, the efficacy and safety of five biological therapies targeting IL-6, namely sirukumab, olokizumab (CDP6038), C326, PF04236921 and BMS-945429, and one compound targeting IL-6R, namely tocilizumab, are investigated in clinical trials.

Sirukumab

Sirukumab (CNT0136) is an investigational human monoclonal IgG1 kappa antibody targeting IL-6 which is currently in Phase III studies tested for the treatment of moderately to severely active rheumatoid arthritis (RA). A previous phase I study demonstrated that sirukumab exerts a well-tolerable safety profile, desirable pharmacokinetic characteristics and a low incidence of immunogenicity following an intravenous infusion in healthy subjects[47]. In phase II studies, sirukumab significantly improved RA signs and symptoms, as measured by the American College

of Rheumatology 50 (ACR50) response at week 12, the primary study endpoint, and treatment with sirukumab was generally well tolerated.

Olokizumab

A further highly potent anti–IL-6 monoclonal antibody, namely olokizumab (CDP6038), selectively stops the final step in the IL-6 signaling complex assembly. Several phase II trials of olokizumab were recently completed, but results have not yet been finally reported. The first evaluated CRP suppression with a single intravenous or subcutaneous dose of olokizumab in patients with active RA, despite therapy with MTX. The second evaluated the safety, efficacy, pharmacokinetics, and immunogenicity of various doses of olokizumab in comparison with placebo and also tocilizumab as add-on treatments to MTX in RA patients with an inadequate response to MTX and TNF inhibitors. This phase 2b study met its primary endpoint of demonstrating a significant reduction in the disease activity score at week 12 across all olokizumab dose groups relative to placebo. Still ongoing is a phase II, open-label, long-term (up to 5 years) study of subcutaneous olokizumab in patients with active RA and inadequate response to MTX. Side effects reported in a phase I trial in healthy volunteers that were considered related to olokizumab included headache, reduced neutrophil and leukocyte counts, and small increases in ALT level.

C326

A further approach to target IL-6 is C326, an Inhibitor of IL-6, which is currently investigated in a phase I study in adults with CD. C326 is a heterotetrameric avimer (binding protein), which is composed of a fusion of the IgG binding domain to the N-terminus of the IL-6 binding trimer. By a placebo-controlled study design safety, pharmacokinetics, pharmacodynamics and immunogenicity of C326 will be assessed in CD patients.

PF-04236921

The fourth anti-IL-6 medication is called PF-04236921 which is a monoclonal, fully human IgG2 antibody targeting IL-6 and therefore inhibiting IL-6 induced signaling. It is currently under investigation in phase II trials in patients with CD, RA and systemic lupus erythematodes (SLE). Preclinical data and first observations in healthy volunteers as well as patients with RA demonstrated a good safety profile of PF-0426921. In particular, with respect to CD, there is a double-blind, randomized, placebo-controlled study ongoing that evaluates efficacy and safety of PF-04236921 in CD patients who are non-responders to anti-TNF treatment (ANDANTE trial) as well as a phase II open label extension trial. Here, PF-04236921 will be tested as a possible treatment for the induction and maintenance of remission in patients with moderate to severe CD that have failed to response to anti-TNF therapy.

BMS-945429

Additionally, BMS-945429 is a fully humanized monoclonal antibody targeting free IL-6 and soluble IL-6R/IL-6 complex. In a phase IIa study in patients with moderate to severe RA, BMS-945429 was efficient to improve the signs and symptoms of RA as measured by ACR responses. Further, the agent was well tolerated. The efficacy of BMS-945429 is currently investigated in clinical phase II trials in patients with moderate to severe CD who had an insufficient response to conventional therapy or had failed anti-TNF treatment.

Anti Interleukin-12/anti-Interleukin-23 strategies

Recent genome wide association studies revealed that polymorphisms within the gene encoding IL-23 receptor (IL-23R) protect from CD[48]. IL-12 and IL-23 consist of a dimer consisting of the common p40 subunit and of a unique subunit, namely p35 for IL-12 and p19 for IL-23. IL-12 and IL-23 are mainly produced by dendritic cells and are crucial for induction and maintenance Th1 (IL-12) and Th17 (IL-23) responses[49]. Blocking IL-12 has been demonstrated to reduce the extent of TNBS-induced colitis in the mouse model and IL-23 seems to be the driving force for inflammation in a RAG-deficient mouse model of colitis[50, 51] making the IL-12/IL-23 axis another promising target for the treatment of IBD. Several drugs inhibiting

the IL-12/IL-23 axis are currently under investigation, namely ustekinumab, briakinumab, apilimod mesylate, AMG139 and SCH-900222.

Ustekinumab

Ustekinumab is a fully human IgG1 monoclonal antibody targeting the p40 subunit of IL-12/IL-23 and is already approved for the treatment of moderate to severe plaque psoriasis. In a phase II trial including 104 patients with moderate to severe CD, clinical response rates to ustekinumab were significantly higher at weeks 4 and 6 following treatment with ustekinumab than with placebo (53% *vs.* 30%). However, at the primary endpoint, week 8, these differences were no longer significant (49% *vs.* 40%). Nevertheless, in the subgroup of patients that had previously failed to respond to anti-TNF therapy, week 8 response was significantly higher in patients receiving ustekinumab than in patients receiving placebo (59% *vs.* 26%)[52]. A recent, larger randomized, placebo-controlled phase IIb trial investigated whether ustekinumab induces clinical response at week 6 as primary end point in a collective of 526 patients with moderate to severe CD who did not respond to infliximab[53]. At week 6, a significantly higher number of patients treated with ustekinumab showed a clinical response compared to patients treated with placebo (39.7% *vs.* 23.5%). To those patients who responded to ustekinumab at week 6 were given maintenance therapy. A significant number of these patients showed a clinical response (69.4% *vs.* 42.5%) and was in remission (41.7 *vs.* 27.4%) at week 22 compared to patients receiving placebo[53]. This indicates that patients with TNF-

refractory moderate to severe CD have a better response rate to ustekinumab. Further, patients with an initial response to ustekinumab have significantly better rates of response and remission with ustekinumab used as maintenance therapy as compared to control patients[53]. In general, ustekinumab was well tolerated. Therefore, ustekinumab seems to be a promising option in patients with TNF-refractory CD and additional phase III trials in patients with moderate to severe CD are ongoing.

Briakinumab

A further fully human monoclonal antibody to the p40 subunit of IL-12 and IL-23 is called briakinumab. In a phase II trial in 79 patients with moderate to severe CD, briakinumab treatment resulted in clinical response in 75% of patients compared to 25% of patients treated with placebo. However this difference was no longer significant at week 18[54]. In a subsequent, larger phase II trial including 230 patients with moderate to severe CD, the rates for clinical remission at week 6 and week 24 for briakinumab-treated patients were not significantly higher than those for patients treated with placebo[55]. An explanation for the different outcome of clinical trials using anti-IL-12/23 antibodies might be that ustekinumab and briakinumab display different binding capacities to the p40 subunit of IL-12/23. Further, the discrepancy might be due to the fact that ustekinumab and briakinumba are immunologiclally rather different molecules. While ustekinumab is a fully human IgG1,κ antibody generated in human immunoglobulin transgenic mice, briakinumab is a recombinant exclusively human-sequence IgG1,λ monoclonal antibody isolated from human phage

display library. These differences might, at least in part, explain the different trial outcomes of those two molecules.

Apilimod mesylate

Apilimod mesylate is an orally administered small molecule that inhibits the transcription of IL-12 and IL-23. An initial phase I/IIa trial in patients with moderate to severe CD showed a clinical activity of the agent[56]. However, a following placebo-controlled, randomized phase II trial in 220 patients with moderate to severe CD revealed that apilimod mesylate has no significant effect on the induction of a clinical response at day 29 when compared to placebo. The trial was finally stopped by the Data Monitoring Committee[57].

AMG139

The safety and tolerability of AMG139, a human monoclonal antibody targeting the p19 subunit of IL-23 while sparing IL-12 and is currently investigated in phase I trials in patients with mild to severe CD.

SCH900222

SCH900222 targets the p19 subunit of IL-23 and is currently under investigation in phase II/III trials in patients with plaque psoriasis.

Anti Interleukin-13 strategies

The Th2-related cytokine IL-13 is mainly produced by T-cells and natural killer cells (NK-cells). It seems to play a critical role for the development of UC, since it impairs epithelial barrier function and induces epithelial cell apoptosis. In the oxalozone-induced mouse model of colitis, IL-13 is necessary for the development of inflammation and blockade of IL-13 ameliorates the extent of colitis. Further, lamina propria T-cells from UC patients produce clearly more IL-13 upon stimulation than those form CD patients[16, 58, 59, 60]. Inhibition of IL-13 production by administration of IFN-$\beta 1\alpha$ in patients with UC ameliorated colitis[61]. These observations suggest that IL-13 plays a pivotal role for the pathogenesis of UC and make it a plausible target for the treatment of UC. Interestingly, a recent study also demonstrated a significant expression of IL-13 along the tracts of CD-associated fistulae and suggested an important role for IL-13 in the pathogenesis of CD-associated intestinal fistulae[62].

QAX576

Consequently, QAX576, a human monoclonal antibody targeting IL-13 is tested in a phase II study to assess its efficacy, safety and tolerability in the treatment of perianal fistulas in CD patients.

Anrukinzumab and tralokinumab

Anrukinzumab, a humanized monoclonal antibody targeting IL-13, as well as tralokinumab (CAT-354), a recombinant human monoclonal antibody directed against IL-13, are currently tested in phase II studies in patients with moderate to severe UC.

Lebrikizumab

Additionally, the anti-IL-13 antibody lebrikizumab was successful in phase II studies in patients with severe asthma [63] and subsequent phase III studies are ongoing.

Anti Interleukin-17 strategies

IL-17, also called IL-17A, is the founding member of the IL-17 family of cytokines (IL-17A-F) and shares the highest homology with IL-17F. IL-17A is the signature cytokine of the recently defined Th17 cell population and is secreted by Th17

cells and innate lymphoid cells (ILCs). However, Th17 cells may also secrete IL-17F, IL-22 and/or IL-23 depending on the cellular context[64].

Elevated levels of IL-17 have been observed in the inflamed intestinal mucosa of patients with CD and UC[65, 66]. Th17 cytokines seem to promote intestinal inflammation by stimulating the secretion of pro-inflammatory cytokines, chemokines and tissue-degrading matrix metallo-proteinases finally resulting in tissue damage[67, 68, 69]. On the other hand, Th17-related cytokines have also been demonstrated to exert protective function in the intestine. These observations are supported by various mouse models of colitis. In example, chronic DSS-induced colitis is aggravated in IL-17A knock-out animals, but ameliorated in IL-17F knock-out mice[70] and IL-17A exerts also a protective role in a T-cell transfer model of colitis[71]. In contrast, in the TNBS-induced murine colitis model, colitis was ameliorated in IL-17 receptor A (IL-17RA) knock-out mice as well as in wild-type mice treated with an IL-17RA IgG1 fusion protein blocking signal transduction via the receptor[15].

The reason for these conflicting results is still unknown. However, it is assumed that the either protective or inflammatory role of Th17 cells in the intestine is dependent on the cytokine milieu during their differentiation and the co-expression of other cytokines, such as IL-10 or IFNγ[64]. Nevertheless, targeting IL-17 has been regarded to be a reasonable approach for the treatment of IBD.

Vidolfludimus

Vidofludimus, a small molecule inhibitor of the expression of both, IL-17A and IL-17F, has shown promising results in an open label, uncontrolled phase II trial including patients with either steroid-dependent UC or CD[72]. After administration of vidofludimus for 12 weeks to 26 steroid-dependent UC or CD patients, 8 out of 14 CD patients (57.9%) and 6 out 12 UC patients (50%) were in steroid-free clinical remission (complete responders). 4 of 14 CD patients (28.6%) and 5 of 12 UC patients (41.7%) were partial responders, defined as being in remission at a steroid dose equal or lower than the individual patient's threshold dose for relapse. 2 CD and 1 UC patient did not show any response. In general, vidofludimus was well tolerated. Though vidofludimus showed clinical efficacy and a good safety profile in this first IBD trial, further and more defined studies will be needed to obtain more meaningful data[72].

Secukinumab

Secukinumab, a human monoclonal anti-IL-17A antibody, has shown promising results in patients with RA and psoriasis. However, a proof-of-concept study in 59 patients with moderate to severe CD failed and blockade of IL-17A was not only ineffective and associated with disease worsening, but also revealed higher rates of severe adverse events, mainly infections, compared to placebo[73].

Ixekizumab

In addition to secukinumab, Ixekizumab (LY2439821), a humanized monoclonal antibody targeting IL-17A, is giving promising results and currently in a phase III study in patients with psoriasis and a phase II study in patients with RA. However, it remains to be determined whether it could become a therapeutic option in IBD patients.

RG4934

Further, RG4934, a monoclonal IL-17A antibody is currently in phase I/II studies in patients with psoriasis.

Cytokines of the IL-1 family: Anti Interleukin-18 and anti-Interleukin-1 beta strategies

The pro-inflammatory cytokines IL-1β and IL-18 are secreted via a unique intracellular protein complex, called the inflammasome. With respect to IBD, particularly the Nlrp3-inflammasome seems to play a crucial role for maintaining intestinal homeostasis and variations within the gene encoding Nlrp3 are associated with increased susceptibility to CD[74]. Nlrp3 protein provides a cytosolic platform for the assembling of the NALP3 inflammasome, a protein complex which is responsible for maturation and secretion of IL-1β and IL-18[75, 76, 77]. Both of the cytokines exert pro-inflammatory properties and are associated with epithelial repair and

wound healing by the recruitment and activation of immune cells and by the induction of pro-inflammatory cytokines, chemokines and growth factors. IL-1β levels in the colon correlated with disease activity and high levels of IL-1β protein are associated with active inflammatory lesions in IBD patients[78, 79]. Similar, serum levels of IL-18 are also elevated in UC and CD patients and protein expression of IL-18 has been shown to be increased in the intestine of CD patients[80, 81]. These early observations resulted in the assumption that IL-1β and IL-18 might contribute to the onset of IBD, especially since inhibition of IL-18 and IL-1β attenuated colitis in mouse models[82, 83, 84, 85, 86]. However, more recent studies suggested that IL-18 and IL-1β exert an important anti-inflammatory role in the intestine, particularly by promoting tissue repair and restitution in of the ulcerated epithelium[87, 88, 89, 90]. These observations are supported by IL-18, IL-18 receptor and IL-1receptor knock-out mice that are more susceptible to DSS-induced colitis than wild-type animals[91, 92]. Therefore, both cytokines were regarded to be potential targets for the treatment of IBD.

Canakinumab

Canakinumab is a high-affinity human monoclonal anti-IL-1β-antibody and is currently studied in phase I to III studies in patients with diseases such as acute gout[93], RA, juvenile rheumatoid arthritis or osteoarthritis.

XOMA 052

A further anti-IL-1β antibody, XOMA 052 is currently in phase II studies in patients with RA and type II diabetes.

GSK 1070806

GSK 1070806 is a humanized monoclonal antibody targeting IL-18 which is currently studied in a phase I trial in healthy and obese subjects.

Anti-IL-22 and anti-IL-5 strategies

IL-22 is a further cytokine that is produced by Th17 cells and elevated levels of IL-22 have been observed in the intestinal mucosa of CD patients. Additional data suggest that IL-22 is also produced by a different T-cell type, by some investigators called Th22 cells[94]. On a functional level, IL-22 increases proliferation and migration of intestinal epithelial cells and enhances the expression of pro-inflammatory mediators, such as TNF-alpha or IL-8. Further, IL-22 is involved in regulating human defensin expression and mucus production[95]. However, recent studies also suggested a protective role for IL-22 in mouse models of colitis[96, 97].

Fezakinumab, a monoclonal anti-IL-22 antibody has recently completed phase I and phase II studies for psoriasis and RA, respectively. It could be interesting to study, whether it might also an option for the treatment IBD patients.

IL-5 is regarded to be a Th2 cytokine and isolated lamina propria mononuclear cells from UC patients produce more IL-5 than those of control and CD patients upon stimulation[16, 98, 99]. In the oxazolone-induced colitis mouse model, which is a model of close to human UC, increased levels of IL-5 are one of the driving forces of the disease suggesting IL-5 could also be a target for treatment of IBD, particularly UC. Mepolizumab and Reslizumab are humanized monoclonal anti-IL-5 antibodies which are currently in phase III studies in patients with asthma and eosinophilic esophagitis.

Anti- C-X-C motif chemokine 10 (CXCL10) strategies

CXCL10, which is also known as interferon inducible 10-kd protein (IP-10), is secreted by various cell types, such as monocytes, endothelial cells and fibroblasts in response to IFNγ[100]. CXCL10 is important for chemo-attraction of monocytes/macrophages, T-cells, NK-cells and dendritic cells to sites of inflammation. Further, it promotes T-cell adhesion to endothelial cells and exerts anti-tumor

effects[101, 102]. CXCL10 inhibits proliferation of endothelial and epithelial cells[103].

In a recent phase II study MDX-1100, a human monoclonal anti-CXCL10 antibody, demonstrated clinical efficacy in RA patients who did not respond to methotrexate and revealed an acceptable safety profile[104]. In a placebo-controlled trial in patients with moderate to severe UC, MDX-1100 did not show a significant clinical benefit when compared to placebo in the overall population[105]. However, when data were stratified according to MDX-1100 trough serum levels, there were increasing rates for response, remission and mucosal healing with increasing MDX serum levels. Unfortunately, also the rates for infections and serious infections increased by increasing MDX serum concentrations. Currently, phase II trials in patients with UC and CD are ongoing.

Human recombinant IL-10

IL-10 is produced by T-cells, B-cells, macrophages/monocytes activated and dendritic cells. It inhibits cytokine production by Th1-cells when they are activated under conditions requiring the presence of antigen presenting cells. IL-10 strongly reduced antigen specific human T-cell proliferation by diminishing the antigen presenting capacity of monocytes via down-regulation of class II MHC expression. In addition, it inhibits cytokine production by activated macrophages, e. g. LPS-induced

expression of IL-1α, IL-6, or TNF. It thus plays not only a role in the regulation of T-cell activation, but also in the down-regulation of acute inflammatory responses[106].

Recent interest in IBD research has focused on the anti-inflammatory properties of IL-10. The important role of IL-10 for immune homeostasis in the gut has been demonstrated by IL-10 deficient mice, which develop chronic entero-colitis which can be prevented by administration of IL-10. The down-regulation of IBD mononuclear phagocyte activation by IL-10 in vitro has recently been demonstrated and recent study linked variation within the gene, encoding the IL-10 receptor with increased susceptibility for IBD[107, 108, 109]. In animal experiments, IL-10 administration was able to prevent colitis, but was ineffective to attenuate already established colitis[110, 111]. Interestingly, adenoviral vector-based strategies of IL-10 gene transfer have been shown to improve symptoms of colitis and RA in respective animal models[6, 112, 113, 114, 115, 116, 117].

The anti-inflammatory effect of IL-10 on mucosal inflammation has been found in vivo when patients with ulcerative colitis received IL-10 enema treatment. Patients with steroid refractory ulcerative colitis treated with IL-10 enemas showed a progressive down-regulation of peripheral monocyte pro-inflammatory cytokine secretion and a clinical improvement[118, 119]. Additionally, in a first trial in patients with steroid-refractory CD, 50% of patients receiving recombinant IL-10 subcutane-

ously achieved remission compared to 23% of patients in the placebo group [119]. However, in large trials assessing the effect of recombinant IL-10 in patients with mild to moderate CD, no significant advantage in achieving clinical remission in response to subcutaneous, recombinant IL-10 was noted in 329 steroid-refractory patients when compared to placebo, while therapy was well tolerated in general[120, 121]. Recombinant IL-10 also was not sufficient to prevent the recurrence of inflammation in CD patients who had undergone ileal or ileocolonic resection[122]. The disappointing observations could have a number of possible explanations: the administered dose of IL-10 may have been too low (however it is limited by side effects) and/or the application form was ineffective (subcutaneous administration with only little of IL-10 reaching sites of active inflammation), IL-10 might only be sufficient for preventing, but not for improving active inflammation (as suggested by the animal experiments), administration of IL-10 alone is not sufficient to block the expression of all of the important, pro-inflammatory mediators and the immuno-stimulatory effects of IL-10, in particular on B-cells and on IFNγ production, may abrogate its anti-inflammatory effects[123].

To address these issues, several methods have been developed. One method was to design genetically engineered *Lactococcus lactis* bacteria that can be administered orally and transport the IL-10 directly to the sites of inflammation. Though this approach seems to be safe, it finally failed to show clinical activity in phase II studies[124]. A further approach might be the rectal application of gelatine

microspheres containing interleukin-10, which has been shown to be effective in mouse models[125]. Gene therapy using replication-deficient adenoviral vectors to deliver the IL-10 gene directly to gastrointestinal epithelial cells also has been suggested. Such a route of administration has already been shown to be effective in a murine model of RA[126].

Human recombinant IL-11

Similar to IL-10, IL-11, a cytokine mainly produced by bone marrow stromal and other mesenchymal cells, also exerts anti-inflammatory effects in the intestine[127]. IL-11 modulates Th1/Th2-type cytokine production from activated T-cells and protects the intestinal mucosa[128, 129, 130]. Further, IL-11 is able to impair the lipopolysaccharide-induce secretion of pro-inflammatory mediators from macrophages/monocytes[131]. A polymorphism within the IL-11 gene is associated with increased susceptibility for UC[132].

In early trials, subcutaneously administered IL-11 appeared to be safe and efficient in about one third of CD patients[133, 134]. However, in a further trial, IL-11 was significantly inferior when compared to prednisolone with respect to response rate and rate of short-term remission in 51 patients with active CD[135].

Human recombinant IFNβ

A further approach using recombinant biologics molecules for treating IBD is the administration of the type I interferon, IFNβ. These cytokine are widely expressed and play a crucial role for innate anti-viral immune responses, but have also a critical effect in the modulation of the anti-inflammatory host response[136]. In mouse models of arthritis, IFNβ exerts anti-inflammatory properties by suppressing the secretion of pro-inflammatory cytokines and chemokines, such as TNF, IFNγ, IL-6, IL-12 or CXCL8 and by stimulating the secretion of the anti-inflammatory IL-10[137, 138, 139, 140].

In a first study, where it was also administered subcutaneously, IFNβ showed a very promising remission rate for about 88% with a mean remission length of about 13 months in patients with steroid-refractory UC[141]. Subsequent randomized, placebo-controlled studies also suggested that IFNβ could exert some beneficial effects in UC patients, however the results were clearly not as good as in the initial trial[61, 142, 143]. Nevertheless, some studies even suggested that IFNβ does not have superior therapeutic effect in UC patients when compared to placebo[144, 145]. Of note, the remission rates of IFNβ were always higher when compared to placebo. However, sometimes these differences were not statistically significant.

In a recent study in patients with CD there was also no significant effect in favor of IFNβ when compared to placebo[146]. Further data suggest that the anti-inflammatory effect of IFNβ is due to the inhibition of IL-13 production[61]. Though in all of the conducted trials, IFNβ revealed to be safe and well tolerable there are

recent case reports that IFNβ treatment in patients with multiple sclerosis was associated with development of IBD[147]. Recent data suggested that IFNγ administration exacerbated colitis in a mouse model of colitis[148]. While the data of the two most recent trials using IFNβ in patients with UC have not been published to date, their results will be of great interest.

New biologicals directed against cytokine receptors

Besides the inhibition of cytokines by antibodies the targeting and inhibition of the respective cytokine receptor represents an additional mechanism how cytokine-induced signaling and consecutive effects can be blocked efficiently. With respect to IBD, inhibition of the receptors for IL-2, IL-6, IL-17 and IL-21 as well as of the chemokine (C-C motif) ligand 25 (CCL25), namely C-C chemokine receptor type 9, has gained interest.

Anti-IL-2-receptor (IL-2R) strategies

IL-2 is a pleiotropic cytokine that is produced by T-cells upon antigen-binding to the T-cell receptor (TCR) and plays an important role in the differentiation and proliferation of naive T-cells into effector T-cells. Activation of TCR results in se-

cretion of IL-2 and the expression of the IL-2R on the surface of the T-cells[149, 150]. The interaction between IL-2 and the IL-2R finally stimulates growth, differentiation and survival of antigen-specific $CD4^+$ and $CD8^+$ cells[151]. IL-2 hereby is crucial for the development of memory T-cells (that display the immunologic memory of the body) as well as for the maturation and differentiation of regulatory T-cells (Tregs). Tregs prevent autoimmune diseases by preventing other T-cells from recognizing and reacting against self-antigens which means that IL-2 is required to discriminate between self and non-self[152, 153, 154]. Of note, recombinant IL-2 is approved for the treatment of malignant melanoma and renal cell cancer.

Basiliximab

Recent studies suggest that the use of anti-IL-2R treatment could be beneficial in the therapy of UC. In initial pilot studies, the anti-IL-2R antibody, basiliximab showed clinical efficacy in patients with steroid-resistant UC. Nine out of 10 patients achieved clinical remission at week 8. However, 8 out of these 9 patients relapsed, but remission could be re-achieved by administration of corticosteroids and azathioprine. After 24 weeks, 7 patients were in full remission and, in the presence of basiliximab, patients became again sensitive to steroids[155]. In a further open-label trial, steroid-resistant UC patients were treated with a single dose of basiliximab in combination with steroids. Here, 65% of the patients achieved clinical remission at week 24[156]. In general, basiliximab treatment was well tolerated. However, a very recent, placebo-controlled study including 149 patients with moderate to severe UC

demonstrated that basiliximab does not increase efficacy of corticosteroids in patients with steroid-refractory UC. The remission rates in the basiliximab groups were even slightly lower than those in the placebo group[157].

Daclizumab

A further anti-IL-2R antibody, namely daclizumab[158], revealed also some clinical benefit in a pilot study in patients with refractory UC. However, in a subsequent, larger, randomized trial including 159 patients with moderate UC, treatment with daclizumab did not result in increased rates of clinical remission at week 8 compared to placebo[159]. Similar to basiliximab, daclizumab was also well tolerated.

Anti-IL-6-receptor (IL-6R) strategies

Tocilizumab

Anti-IL-6 antibodies seem to be a reasonable approach for the treatment of IBD (see above). A further possibility to inhibit IL-6 mediated effects is the blockade of the IL-6R. Tocilizumab is a monoclonal anti-IL-6R antibody that is already approved as second line therapy for the treatment of RA. To date, only the data from one placebo-controlled phase I trial in 36 patients with active CD are available. Here, 80% of the CD patients treated with tocilizumab showed a clinical response com-

pared with 31% of patients in the placebo group. Only 20% of the tocilizumab-treated patients went finally in remission[160]. Adverse events were comparable in the tocilizumab and placebo group. Data from RA patients suggest that tocilizumab treatment increases the incidence of grade III neutropenia, infections, abnormal liver function and elevated lipids. Though these adverse events are generally mild and are resolved upon treatment, especially the long-term effects of the latter two observations have to be further explored[161, 162]. A further anti-IL-6R antibody, namely sarilumab, is currently in phase II and III studies in patients with RA and ankylosing spondylitis.

Anti-IL-17-rerceptor (IL-17R) strategies

Though results for inhibition of IL-17 were not convincing, inhibiting the IL-17R has been considered to be a worthwhile approach for IBD treatment. In example, brodalumab, a human anti-IL-17R monoclonal antibody, has been shown to improve moderate-to-severe plaque psoriasis in a large, randomized and placebo-controlled phase II study[163].

Anti-IL-21-receptor (IL-21R) strategies

IL-21 is also a member of the IL-17 cytokine family and exerts potent regulatory effects on immune cells, including NK-cells and cytotoxic T-cells. IL-21 induces cell division and proliferation in its target cells[164, 165]. Further, IL-21 is ex-

pressed in NK-cells and activated $CD4^+$ T-cells and IL-21 expression is up-regulated in Th2 and Th17 cells as well as T follicular cells[166, 167, 168]. In particular, ATR-107 (PF05230900) is an IL-21R antagonist that is currently tested in phase I studies.

Anti-C-C chemokine receptor type 9 (CCR9)

CCR9 is the receptor for CCL25 and seems to play a pivotal role for leukocyte homing to the gut mucosa. While CCR9 is expressed on T-cells and plasmacytoid dendritic cells, it ligand can only be detected in the small intestine, but neither in the caecum nor the colon. CCR9 is important for the attraction of these cells to the lamina propria. In contrast, homing of $CD4^+$ T-cells to the lamina propria of the small intestine seems to be less dependent on CCR9[169, 170, 171, 172]. In a mouse model of colitis, the sites of inflammation coincide with the with the location of CCL25 expression and the number of $CCR9^+$ T-cells increases with disease progression reaching a peak at the time point when most severe inflammation can be observed[173]. However, in this model of inflammation, blockade of either CCL25 or CCR9 was only effective in early stages of the disease development[174]. In a further colitis mouse model, deficiency of CCL25 or CCR9 did not have any effect on disease development or progression[175]. However, it has also recently been demonstrated that CCL25-CCR9 signaling is important for the migration of Tregs into the intestinal mucosa and administration of a CCL9-antibody exacerbated inflammation in a mouse model of ileitis[176].

CCX282-B

CCX282-B is a small molecule inhibitor of CCR9 that blocks migration of gut-specific T-cells[177]. In a recent, double-blind and placebo-controlled phase II study in patients with moderated to severe CD, CCX282-B was well tolerated and safe, since no drug related adverse events, particularly no serious or opportunistic infections, were detected during the 36-week maintenance study period. Though there was no significant difference in achieving clinical response at week 8, the primary end-point of the study, there was a significant difference in achieving clinical response at week 12 between patients receiving CCX282-B and placebo. The trial also revealed that following the induction of remission by CCX282-B, in about 50% of the patients remission was maintained at week 36, while in placebo-treated patients, remission rates continuously declined. Further, a smaller number of patients treated with CCX282-B needed steroid rescue therapy when compared to the placebo group. Currently, the effect of CCX282-B is studied in phase III trials in CD patients.

New drugs directed against cytokine signal transduction

Besides targeting the cytokine or a cytokine receptor directly, a third approach to prevent or inhibit cytokine-mediated inflammation is to inhibit the cytokine-receptor associated signaling pathways. This way, cytokine-induced signaling is inter-

rupted and the respective effects are prevented. An important signaling intermediate of a large number of cytokine receptors are the member of the Janus kinase family (JAK) 1, 2 and 3. These JAK-molecules play a crucial role in cytokine-mediated cell growth, survival, development and differentiation of immune cells. While JAK1 and JAK3 are expressed in a variety of cell types, JAK3 is restricted to hematopoietic cells. Further, JAK3 is involved in the signaling pathways induce by IL-2, IL-4, IL-7, IL-9, IL-15 and IL-21[178].

Tofacitinib is a first-in-class small-molecule JAK3 inhibitor. Its efficiency is currently investigated in a broad range of inflammatory disorders, such as CD, UC or RA[179]. In *in vitro* studies, tofacitinib has been demonstrated to prevent pathologic immune phenomena by blocking the production of IL-17, IL-22 and IL-23R effectively. Further, tofacitinib impairs the activation of STAT1 and T-bet transcription factor what finally suppresses the differentiation of Th1, Th2 and Th17 cells[180]. In a clinical phase II trial including 139 patients with moderate to severe CD that were randomized to receive one of three doses of tofacitinib or placebo, the primary end point, clinical response at week 4, was not achieved. However, there was a significant reduction in serum CRP levels and fecal calprotectin levels in patients receiving the highest dose of tofacitinib and the drug was in general well tolerated [181]. In a phase II trial including 194 patients with moderate to severe UC, that were randomized to receive one of four doses of tofacitinib or placebo, tofacitinib reached its primary endpoint, which was clinical response at week 8. The clinical response rates in the patient groups receiving the two highest tofacitinib doses were 61%-78% com-

pared to 42% in the placebo group. Clinical remission rates at week 8 were 41% and 49%, respectively, for the patient groups receiving the highest tofacitinib doses (10% in the placebo group). In general, tofacitinib was well tolerated[182]. These observations strongly indicate the plausibility of further studies using tofacitinib in IBD patients.

Summary and outlook

In the last few years, a large number of new approaches targeting cytokines and chemokines for treating IBD patients have been developed. However, only a small number of them seem to be really promising for daily clinical practice. In particular ustekinumab, an antibody directed against the IL-12/IL-23 axis generated very promising results in clinical trials and will most likely be approved for the treatment of CD patients soon. In addition, new anti-TNF approaches, antibodies against IL-6 or IL-6R as well as tofacitinib, a small molecule inhibitor of the cytokine signal transmitter Jak3, seem to be very promising approaches for the treatment of IBD patients and are likely to be the next series of medications being approved for this complex disease. A number of further anti-cytokine antibodies are currently in early phase clinical trials and their efficacy in IBD patients has still to be determined (Figure 2). Considering all of the new anti-cytokine approaches, it looks like treatment options for IBD patients, and in particular for such patients that are non-responding to currently established treatments, will be essentially improved in the near future.

However, the efficacy and safety of all of these new medications in uncontrolled patient populations and their use in daily clinical practice has still to be determined.

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Conflict of interest

G.R. has consulted to Abbott Switzerland and Abbott International, Tillots International, to FALK Germany, to Essex/MSD Switzerland, Novartis, Roche, and Vifor Switzerland; has received speaker's honoraria from Abbott, FALK, MSD, Phadia, Tillots, UCB, and Vifor; and has received educational grants and research grants from Abbott, Ardeypharm, Essex/MSD, FALK, Flamentera, Novartis, Tillots, UCB and Zeller. S.R.V. discloses grant support from Abbott, Tillots, UCB and MSD. MS received speaker's honoraria from FALK.

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Figure legends

Figure 1. Cytokines and cytokine-associated molecules as current drug targets for the treatment of IBD. The image shows the targets as well as the pharmaceutical agents for treatment of IBD that are currently studied in clinical trials in IBD patients

Figure 2. The pipeline of anti-cytokine medications for the treatment of IBD.

Tables

Agent	Company	Target	Indication	Trials	Phase	Other indications
TNF-Kinoid	Neovacs	TNF	CD	ongoing	3	
DLX105	Delenex	TNF	CD	ongoing	2	Osteoarthritis II
Golimumab	Johnson and Johnson	TNF	UC	ongoing	3	
C326	QPharm	IL-6	CD	ongoing	1	
PF 04236921	Pfizer	IL-6	CD	ongoing	2	
BMS945429	BMS	IL-6	CD	ongoing	2	
Ustekinumab	Centocor	IL-12/23	CD	ongoing	3	
AMG139	Amgen	IL-23	CD	ongoing	1	

QAX576	Novartis	IL-13	CD	ongoing	2	
Anrukinzumab	Pfizer	IL-13	UC	ongoing	2	
Tralokinumab	Astra Zeneca	IL-13	UC	ongoing	2	
Vidofludimus	4SC AG	IL-17A+F	CD+UC	ongoing	2	
MDX-1100	Medarex	CXCL10 (IP-10)	CD, UC	ongoing	2	
IFNβ recom-binant		IFNβ	UC, CD	ongoing	3	
Tocilizumab	Roche	IL-6R	CD	ongoing	1	
CCX282-B	GSK	CCR9	CD	ongoing	3	
Tofacitinib	Pfizer	Jak-3	CD, UC	ongoing	2	
Briakinumab	Abbott	IL-12/23	CD	failed	2	
Apilimod me-sylate	Synta Phar-maceuticals	IL-12/23	CD	failed	2	
Secukinumab	Novartis	IL-17A	CD	failed	2	
IL-10 recom-binant	Schering-Plough	IL-10	CD	failed		
IL-11 recom-binant		IL-11	CD	failed		
Daclizumab	Facet Bio-tech	IL-2R	UC	failed		
Basiliximab	Cerimon Pharmaceu-ticals	IL-2R	UC	failed		
Ozoralizumab	Pfizer	TNF		no IBD trials	2	RA II
Sirukumab	GSK	IL-6	-	no IBD trials	-	RA, phase III
Olokizumab	UCB	IL-6	-	no IBD trials	-	RA II
SCH900222	Merck & Co	IL-23		no IBD trials	1-2	Psoriasis
Lebrikizumab	Roche	IL-13	-	no IBD trials	-	Asthma

Ixekizumab	Eli-Lilly	IL-17A	-	no IBD trials	-	Psoriasis, phase III
RG4934	Roche	IL-17A	-	no IBD trials	-	Psoriasis, phase II
GSK 1070806	GSK	IL-18	-	no IBD trials	-	Healthy and obese subjects, phase I
Canakinumab	Novartis	IL-1β	-	no IBD trials	-	Approved, acute gout
XOMA 052	XOMA	IL-1β	-	no IBD trials	-	RA, phase II
Fezakinumab	Pfizer	IL-22	-	no IBD trials	-	RA, phase II
Reslizumab	Cephalon	IL-5	-	no IBD trials	-	Asthma, phase III
Mepolizumab	GSK	IL-5	-	no IBD trials	-	Asthma, phase III
Sarilumab	Sanofi	IL-6R	-	no IBD trials	-	RA, phase II
Brodalumab	Amgen	IL-17R	-	no IBD trials	-	Psoriasis, phase II
PF 05230900	Pfizer	IL-21R	-	no IBD trials	-	Phase I

Table 1: The therapeutic pipeline in IBD.